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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,839	FUKUNAGA ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/20/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,12,13,17-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,12,13,17-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment and remarks submitted on March 20, 2007. Claims 9, 12-13, 17-20 and 22-25 are pending in the application and are being examined on the merits herein.

Applicants' arguments regarding the rejections of the claims have been fully considered but they are not persuasive. The following rejections have been necessitated by Applicants' amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 12-13, 17-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the specification as originally filed does not provide support for the recitation that the

hydroxypropyl cellulose is "containing 53.4-77.7% of hydroxypropyl group," as recited in newly amended claim 9. The specification provides support for hydroxypropyl celluloses containing "53.4 to 77.5%" of a hydroxypropyl group (see page 7, lines 1-7, in particular), but does not teach the celluloses containing up to 77.7% of the hydroxypropyl group, as recited in the claim. Accordingly, claim 9 recites impermissible newt matter and is rejected under 35 U.S.C. 112, first paragraph. Claims 12-13, 17-20 and 22-25 are rejected as being dependent upon a claim having new matter recited therein.

Claim 25 is furthermore rejected under 35 U.S.C. 112, first paragraph, because the specification as originally filed does not provide support for the viscous preparation that "retains bFGF activity at 25°C at a remaining ratio of 98% for at least 42 hours," as recited in the newly added claim. The specification discloses that for the particular preparations 1a and 1b having a specific content of thickener and bFGF, that a remaining ratio remaining after 42 hours was 99.1 and 98.9 (see Table I, in particular.) The specification does not teach that a remaining ratio was 98% for all viscous preparations in general, having and content of the bFGF and hydroxypropyl cellulose. Accordingly, claim 25 recites impermissible new matter, and is rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 and 12-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,046,164 to Asano et al, issued April 4, 2000, in view of EP 0 267 015 to Amy L. Finkenaur, published May 11, 1988.

Asano et al. teaches a method for treating diseases of periodontal tissue by administering a basic fibroblast growth factor (see abstract, in particular.) Asano et al. teaches that the bFGF can be prepared in various formulations, including liquids by combining bFGF with a pharmacologically acceptable additive, such as a solvent, stabilizer, etc. (see column 4, lines 4-15, in particular.)

Asano et al. does not specifically teach providing hydroxypropyl cellulose in the bFGF composition, as recited for example in claim 9.

Finkenaur teaches that a stabilizing effective amount of a water-soluble polysaccharide can be provided in medicinal compositions containing a polypeptide growth factor with mitogenic activity to stabilize the polypeptide growth factor against

loss of biological activity in the presence of moisture (see abstract, in particular.) Finkenaur teaches that basic fibroblast growth factor is an example of such as polypeptide growth factor that can be stabilized with the polysaccharide (see page 3, lines 25-30, in particular.) Finkenaur further teaches that the polysaccharides act to increase the viscosity of the composition (see page 4, lines 55-65, in particular), and thus are thickeners. Finkenaur teaches that the stabilizing polysaccharide for stabilizing the polypeptide growth factor can be selected from among polysaccharides including methyl cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose (a hydroxypropyl ether derivative of cellulose), as in claim 9 (see page 3, lines 35-50, in particular.)

Regarding the recitation that hydroxypropyl cellulose contains 53.4-77.7% of hydroxypropyl group, as in claim 9, Finkenaur teaches that the solubility of the cellulose derivatives is determined by degree of substitution of the ether groups, and teaches that a suitable degree of ether substitution may be at least 0.35 ether groups per anhydroglucose unit (see page 3, lines 44-50, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of ether substitution of the celluloses, according to the guidance provided by Finkenaur, to provide a composition having desired properties, such as desired solubility. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover

the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to incorporate the hydroxypropyl cellulose stabilizer/thickener of Finkenaur into the bFGF composition taught by Asano et al. and administer for the treatment of periodontal disease, because Asano et al. teaches that a composition comprising bFGF and a stabilizer can be administered for the treatment of periodontal disease, and Finkenaur teaches that polysaccharides such as hydroxypropyl cellulose (that are also thickeners) act to stabilize bFGF. Thus, one of ordinary skill in the art would have been motivated to provide the polysaccharide of Asano et al. in the bFGF composition of Asano et al. for administration with the expectation of administering a stabilized formulation capable of treating periodontal disease. Therefore, the method of claim 9 is obvious over the teachings of Finkenaur and Asano et al.

Regarding claims 12 and 15, Asano et al. teaches that the bFGF composition can treat periodontitis (periodontosis.) Regarding claims 13-14 and 16, Asano et al. teaches that a suitable content of bFGF in the composition can be from 0.001 to 20%, which is the same as the ranges being claimed. Regarding claim 17, Asano et al. teaches that the composition can be administered for repair of periodontal tissue after

tooth extraction, and for regeneration of dentin defected by dental caries, as recited in the claim.

Regarding claims 18-19, Asano et al. teaches that the bFGF can be combined with pharmacologically acceptable additives, such as a suspending agent, stabilizer or filling material (see column 4, lines 1-13, in particular), and thus teaches that an inactive and non-toxic additive can be provided. Asano et al. also teaches that the bFGF can be combined with a solvent, and the composition can be prepared by a known method such as dissolution of the bFGF. Finkenaur teaches providing a polysaccharide (thickener) in the composition, as discussed above. Accordingly, the references teach providing the preparation in a solution for dissolution with a thickener and an inactive and non-toxic additive as recited in the claims.

Regarding claims 20-21, Finkenaur teaches the stabilized compositions can be in the form of aqueous medicinal compositions (see page 3, lines 55-60, in particular.)

Regarding the viscosity of the preparation as recited in claims 22-24, it is noted that Finkenaur teaches that the polysaccharide stabilizer can be provided to give a desired viscosity, such as a viscosity in the range of 1-5000 cps (see page 4, lines 55-65, in particular), which overlaps and/or encompasses that claimed. Finkenaur teaches that the increased viscosity improves the residence time of the effective concentration of the growth factor (see page 4, lines 55-64, in particular.) Finkenaur also generally

teaches that the amount of cellulose derivative provided can be selected according to the concentration of the growth factor, the type of formulation and the like (see page 3, lines 55-62, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount and/or type of the cellulose derivative stabilizing agent provided in the composition, according to the guidance provided by Asano et al. and Finkenaur, to provide a composition having desired stabilization, viscosity and residence time properties. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claim 25, it is noted that as the combined teachings of Asano et al. and Finkenaur renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely the stable retention of bFGF over a time period, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Response to Arguments

Applicants' arguments filed March 20, 2007 have been fully considered but they are not persuasive.

In particular, Applicants argue that the claimed method of involving administration of a viscous preparation comprising bFGF and the particular polysaccharide that is hydroxypropyl cellulose provides unexpectedly good results. Applicants have previously presented a declaration under 37 CFR 1.132 and signed by Moriyuki Ohkuma that presents a comparison of the stability of bFGF in solutions having various different polysaccharides and other thickeners, including hydroxypropylcellulose, fibrinogen, sodium carboxymethyl cellulose, hydroxypropylmethylcellulose and methylcellulose. Applicants point out that the thickeners fibrinogen and sodium carboxymethyl cellulose resulted in solutions that had either denatured bFGF or were excessively turbid, and thus could not be measured. Applicants further note that the solution having the claimed polysaccharide, namely hydroxypropyl cellulose, exhibited a loss of bFGF after 24 hours of only about 1.3%, whereas the comparison polysaccharides hydroxypropylmethylcellulose and methylcellulose exhibited a loss after 24 hours of about 5.5% and 7.6%, respectively. Applicants thus assert that the viscous preparation having the particular polysaccharide that is hydroxypropyl cellulose and method of use thereof provides unexpectedly good results, including over the polysaccharides such as methylcellulose and hydroxypropylmethyl cellulose that are

taught in the prior art. Applicants further argue that the claims have been amended to recite a particular type of hydroxypropyl cellulose that provides a good comparison to the other formulations.

The Examiner finds these results unpersuasive. It is noted that evidence of unexpected results must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). In the instant case, Finkenaur discloses that the stability of growth factors such as bFGF can be enhanced by providing water soluble polysaccharides, and even teaches that "the hydroxyalkyl cellulose derivatives such as hydroxypropyl cellulose, hydroxyethylcellulose and hydroxypropyl methylcellulose are preferred," (see page 3, lines 35-43, in particular) and thus lists the claimed polysaccharide that is hydroxypropyl cellulose amongst those that are particularly preferred. Accordingly, given Finkenaur's teachings of the enhanced stability imparted by the polysaccharides, it is not deemed unexpected that the claimed hydroxypropyl cellulose imparts good stability to the growth factor bFGF, such as better stability that the thickener fibrinogen. The Examiner notes that it is well established that any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See also MPEP §716.02.

Furthermore, with regards to the magnitude of the stability enhancement for the hydroxypropyl cellulose versus the comparison polysaccharides, namely methylcellulose and hydroxypropyl methyl cellulose, it is noted that Finkenaur teaches the desirability of using *water soluble* cellulose derivatives to impart the stability enhancement, and furthermore teaches that "the solubility of the cellulose derivatives is determined by the degree of substitution (D.S.) of ether groups and the stabilizing derivatives useful in the present invention should have a sufficient quantity of such ether groups per anhydroglucose unit in the cellulose chain to render the derivatives water soluble" (see page 3, lines 44-48, in particular), and thus Finkenaur teaches that the water-solubility and thus stabilization properties of the polysaccharides can vary according to the degree of substitution of the compounds. Furthermore, it is noted that properties such as the length of the polysaccharide can affect the solubility and thus the stabilization properties of the polysaccharide. Accordingly, the fact that a composition having hydroxypropyl cellulose can be prepared to provide an amount of bFGF that reduces by only about 1.3%, and compositions comprising other such water-soluble polysaccharides (methyl cellulose and hydroxypropyl methyl cellulose) can be prepared that result in a greater loss of bFGF, such as 5.5% and 7.6%, is not considered unexpected, as Finkenaur teaches that the solubility, and thus the stabilization properties of the polysaccharide are dependent upon not only the type of polysaccharide used, but also for example upon the degree of substitution of the polysaccharide. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the desired

polysaccharides, and to optimize and/or adjust the degree of substitution of the polysaccharides, as well as other contributing stability factors such as the polysaccharide molecular weight, to provide a composition having the desired stability. Thus, it is considered that Applicants do not provide sufficient evidence of unexpected results in comparison to the closest prior art. See MPEP 716.02(e).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER